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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/777,552	02/12/2004	Daniel A. Hammer	UPN-4290	6019

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EXAMINER	
SCHLIENTZ, LEAH H	
ART UNIT	**PAPER NUMBER**
1618	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/777,552	HAMMER ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-184* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1–5, 10–13, 15–23, 32–42, 46, 52–55, 60–63, 65, 70–75, 78, 79, and 88–101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/20/04 and 11/17/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 6-9,14,24-31,43-45,47-51,56-59,64,66-69,76,77,80-87 and 102-184.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I in the reply filed on 1/16/07 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse and is hereby made final (MPEP § 818.03(a)). Applicant's election of the following species for search purposes are also acknowledged: porphyrin as the emissive moiety, R_A is phenyl, R_B is hydrogen, the linker is ethylyne, the hydrophibic polymer is polybutadiene, and the block copolymer is ethylene oxide/polybutadiene. Claims 1 – 184 are pending, of which claims 107 – 184 have been withdrawn from consideration as being drawn to a non-elected invention, and claims 6 – 9, 14, 24 – 31, 43 – 45, 47 – 51, 56 – 59, 64, 66 – 69, 76, 77, 80 – 87, and 102 – 106 have been withdrawn from consideration as being drawn to non-elected species. As cited by Applicant, claims 1 – 5, 10 – 13, 15 – 23, 32 – 42, 46, 52 – 55, 60 – 63, 65, 70 – 75, 78, 79, and 88 – 101 read on the elected species.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 15, 22, 23, 32 – 42, and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee *et al.* (*Biotechnol. and Bioeng., 2001, 73, p. 135 – 145*).

The above cited reference, hereinafter Lee, drawn to a non-elected species regarding the emissive agent, was found during the search for the elected species (porphyrin). It is not to be interpreted that a comprehensive search was performed for additional non-elected species.

Lee discloses polymersomes made from amphiphilic diblock copolymers, including poly(ethylene oxide) – poly(butadiene) (PEO-PBD). The PEO (i.e. hydrophilic) fraction of the vesicle-forming polymer PEO-PBD is 0.28 (pages 135 – 136). A trace amount of the polarity-sensitive probe, LAURDAN, was mixed with the polymer followed by vesicle formation (page 138). Fluorescence imaging of the vesicles shows that the predominantly hydrophobic fluorophore LAURDAN (i.e. which emits in the visible spectral range) is membrane localized (page 142). Regarding the limitations of claims 32 and 33, the limitations wherein the amphiphilic co-polymer is made by attaching two strands comprising different monomers or is made by free radical initiation, anionic polymerization, etc. appear to be product-by-process type limitations. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a

different process." See *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1 – 4, 15, 22, 23, 32 – 42, 46, 52 – 55, 65, 74, 78, 79, and 88 – 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger 6,123,923) in view of Lee *et al.* (*Biotechnol. and Bioeng., 2001, 73, p. 135 – 145*).

Unger discloses methods for diagnosing the presence of diseased tissue in a patient comprising administering to a patient a composition comprising a stabilizing material and a photoactive agent and scanning the patient using optical imaging and ultrasound imaging to obtain visible images (column 1, lines 34 – 40). The stabilizing

material is a liposome or other vesicle, including vesicles formed from polymers which may be of natural, semi-synthetic, or synthetic origin (column 24, lines 58 – 63 and claims 1 – 4). Preferred synthetic polymers or copolymers are those comprising acrylic acid, ethylene glycol dimethyacrylates, poly(ethylene oxide), etc. (column 25, lines 40+). The photoactive agent is active in a wavelength from about 500 nm to about 1400 nm, including the infrared wavelength (claims 8 and 9). The photoactive agent may be a fluorescent material, and may be a variety of substances, including fluoresceins, porphyrins, metalloporphyrins, benzoporphyrins, etc. (claims 10 – 12). The photoactive agents may be integrated within the wall(s) of the vesicle, for example, by being interspersed among stabilizing materials which are contained within the vesicle layer(s) or wall(s) (column 10, lines 14 – 20). The compositions are used for optical imaging, or the production of visible representations of tissue or regions of a patient with electromagnetic energy in the spectral range between ultraviolet and infrared and analyzing either the reflected, scattered, absorbed and/or fluorescent energy produced as a result of the irradiation (column 6, lines 7 – 17). The compositions may further comprise a targeting moiety, which may be a protein, peptide, etc. (claims 19 – 23).

Unger fails to specifically recite that the polymers or copolymers which are used to form the polymeric vesicles are amphiphilic copolymers, though it is noted that various hydrophilic (i.e. polyethylene glycol) and hydrophobic polymers are exemplified, and copolymers which are combinations thereof (i.e. copolymers which are combinations of hydrophilic / hydrophobic polymers) are possible embodiments of the compositions taught by Unger.

Lee discloses polymersomes made from amphiphilic diblock copolymers, including poly(ethylene oxide) – poly(butadiene) (PEO-PBD). The PEO (i.e. hydrophilic) fraction of the vesicle-forming polymer PEO-PBD is 0.28 (pages 135 – 136), as set forth above. Lee teaches that vesicles made completely from di-block copolymers – polymersomes – can be stably prepared by a variety of techniques common to liposomes. These thick-walled vesicles of polymer can encapsulate macromolecules, just as liposomes, but exhibit no in-surface thermal transitions. Suspension in blood plasma has no immediate ill-effect on vesicle stability (see abstract and pages 140 – 144). The polymersomes may incorporate a fluorophore (i.e. LAURDAN) within the membrane for fluorescence imaging (page 142).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute copolymers of PEO-PBD, which self-assemble to form polymersomes (i.e. polymeric vesicles) as taught by Lee, for the liposomes or polymeric vesicles in the compositions taught by Unger, which also comprise various photoactive agents, including porphyrin and porphyrin derivatives within the vesicle membrane and are used for optical imaging purposes. One would have been motivated to do so because Unger discloses that a variety of vesicles may be employed, and because Lee teaches such polymersomes to be superior to traditional liposomes or "stealth" liposomes (pegylated liposomes) for encapsulation technologies because of their thicker, more robust membranes. The polymersomes were found to be biocompatible and non-toxic in cell culture. Furthermore, the polymersomes were also shown to be

capable of incorporating an emissive agent within the membrane for fluorescence imaging.

Claims 1 – 4, 15, 22, 23, 32 – 42, 46, are rejected under 35 U.S.C. 103(a) as being unpatentable over Klaveness (US 6,159,445) in view of Lee (*Biotechnol. and Bioeng., 2001, 73, p. 135 – 145).*

Klaveness discloses particulate light imaging contrast agents. Preferably, the particles are substantially monodisperse polymer particles which may be modified to carry a chromophore (or fluorophore), preferably having characteristic absorption and/or emission maxima in the 600 to 1300 nm range. Furthermore they may be modified to include or carry a targetting vector, e.g. a species serving to cause the particles to accumulate at a desired target site, for example a drug, antibody, antibody fragment or peptide (e.g. an oligopeptide or polypeptide) which has a binding affinity for sites within the target zone, e.g. cell surface receptors (column 10, lines 9 – 29). The particulate materials may be in the form of liposomes, liposomes covalently bearing PEG moieties, liposomes containing amphiphathic compounds, etc. (column 12 – 14). The photolabel (i.e. chromophore or fluorophore) may be fluorescein, phthalocyanine, porphyrin or porphyrin analogues, particularly fluorophores having an emission maximum at a wavelength above 600 nm (column 16, lines 1 – 20).

Klaveness fails to specifically teach that the vesicles are prepared from amphiphilic copolymers.

Lee discloses polymersomes made from amphiphilic diblock copolymers, including poly(ethylene oxide) – poly(butadiene) (PEO-PBD). The PEO (i.e. hydrophilic) fraction of the vesicle-forming polymer PEO-PBD is 0.28 (pages 135 – 136), as set forth above. Lee teaches that vesicles made completely from di-block copolymers – polymersomes – can be stably prepared by a variety of techniques common to liposomes. These thick-walled vesicles of polymer can encapsulate macromolecules, just as liposomes, but exhibit no in-surface thermal transitions. Suspension in blood plasma has no immediate ill-effect on vesicle stability (see abstract and pages 140 – 144). The polymersomes may incorporate a fluorophore (i.e. LAURDAN) within the membrane for fluorescence imaging (page 142).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute copolymers of PEO-PBD, which self-assemble to form polymersomes (i.e. polymeric vesicles) as taught by Lee, for the liposomes or polymeric vesicles in the compositions taught by Klaveness, which also comprise various photoactive agents, including porphyrin and porphyrin derivatives, and are used for optical imaging purposes. One would have been motivated to do so because Klaveness teaches that a variety of vesicles may be employed, and because Lee teaches such polymersomes to be superior to traditional liposomes or "stealth" liposomes (pegylated liposomes) for encapsulation technologies because of their thicker, more robust membranes. The polymersomes were found to be biocompatible and non-toxic in cell culture. Furthermore, the polymersomes were also shown to be

capable of incorporating an emissive agent within the membrane for fluorescence imaging.

Claims 1 – 5, 10 – 13, 15 – 23, 32 – 42, 46, 52 – 55, 60 – 63, 65, 70 – 75, 78, 79, and 88 – 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klaveness and Unger in view of Lee, in further view of Lin (*Chem. Eur. J.,* 1995, 1, p. 645 – 651).

Klaveness and Unger disclose compositions comprising liposomes and/or polymeric vesicles comprising a photoactive agent or photolabel, including various fluorophores including porphyrins and porphyrin derivatives, fluoresceins, phthalocyanines, etc, in particular those having an emission maximum at a wavelength above 600 nm, as set forth above. Such compositions taught by Klaveness and Unger are used for optical imaging purposes.

Klaveness and Unger fail to specify that the liposomes, polymer-modified liposomes, or polymeric vesicles comprise amphiphilic copolymers.

Lee discloses polymersomes made from amphiphilic diblock copolymers, including poly(ethylene oxide) – poly(butadiene) (PEO-PBD), which are also capable of incorporating a fluorescing moiety within the polymer membrane, as set forth above. The polymersomes are superior to liposomes in terms of membrane strength.

Lin discloses ethynyl- and butynyl-bridged bis- and tris-(porphinato)zinc chromophores. A variety of points of connectivity joining various (porphinato)zinc moieties via ethynl or butadiene groups, including meso, meso-to-β, or β-to-β linkage

topologies, were investigated. The absorptive and emissive signatures of the supramolecular structures are dramatically modulated by such structural modification. The magnitude of spectral modification attainable with the systems are far greater than that attainable with a single porphyrin chromophore (page 650). For example, the extent of absorptive and emissive modulation possible in the series of such compounds is depicted in Figure 4. Structure 8, in which two ethyne moieties connect three (5,15-diphenylporphinato)zinc macrocycles at meso positions has a B-band FWHM (full width at half maximum) of nearly 5000 cm^{-1}, a Q-band FWHM of 1485 cm^{-1}, absorbs at around 550 nm and 800 nm, and emits at 835 nm (page 649). The supramolecular multiporphyrin complexes may be used in the development of dyes, sensitizers, optical probes, etc. (page 645).

Lin fails to disclose that the ethyne-linked porphyrin moieties are embedded within a polymeric membrane.

It would have been obvious to one of ordinary skill in the art, at the time of the instant invention, to substitute amphiphilic copolymers of PEO-PBD, which self-assemble to form polymersomes (i.e. polymeric vesicles) as taught by Lee, for the liposomes or polymeric vesicles in the compositions taught by Klaveness or Unger, which also comprise various photoactive agents, including porphyrin and porphyrin derivatives within the vesicle membrane and are used for optical imaging purposes. One would have been motivated to do so because Lee teaches such polymersomes to be superior to traditional liposomes or "stealth" liposomes (pegylated liposomes) for encapsulation technologies because of their thicker, more robust membranes. The

polymersomes were found to be biocompatible and non-toxic in cell culture. Furthermore, the polymersomes were also shown to be capable of incorporating an emissive agent within the membrane for fluorescence imaging. It would have been obvious to select ethyne-linked porphyrin moieties as the porphyrin derivative to represent the photoactive agent in the compositions of Klaveness or Unger because Therein teaches such ethynyl- bridged bis- and tris-(porphinato)zinc compounds to have variable absorption / emission spectra depending on structural modification, including those capable of absorbing / emitting around 800 nm, and because such compounds may be employed in optical proves, sensitizers, etc., and because Klaveness teaches the importance of fluorophores which have an emission maximum above 600 nm. One would have been motivated to utilize such ethyne-linked porphyrins as the porphyrin moieties in the compositions of Klaveness, because Klaveness also teaches that the most interesting wavelengths for light imaging techniques are those in the range of 600 – 1300 nm because these wavelengths have the ability to penetrate relatively deeply into living tissue without absorption by natural substances and also are harmless to the human body (column 3, lines 25 – 33).

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LHS

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER